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Determination of the Bioavailability of Novel Antisense Chemistries Using Analogs of a Phosphorothioate Oligonucleotide in Mice

ISIS 7818 C·A·G·C·C·A·T·G·G·T·T·C·C·C·C·C·A·A·C
(2'-OMe)

ISIS 7817 C·A·G·C·C·A·T·G·G·T·T·C·C·C·C·C·A·A·C
(2'-OPropyl)

ISIS 13251 C·A·G·C·C·A·T·G·G·T·T·C·C·C·C·C·A·A·C
(2'-MOE)

Key: A, C, G, T = 2' deoxyribose
A, C, G, T = 2' O-modified ribose
 = phosphorothioate

FIGURE 1

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Effect of 2'- Modifications of Oligonucleotides on Oral Bioavailability¹ in Mice

Oligonucleotide	I.V.		Oral	
	Systemic Tissue ^a (% Dose)		Systemic Tissue ^a (% Dose)	% Bioavailability ^b
7818 (2'-OMe)	18		0.35	1.9
7817 (2'-OPropyl)	22		0.31	1.4
13251 (2'-MOE)	7		1.46	20.9 ^c

^a liver + kidney

^b rat/l.v. x 100

^c may overestimate actual bioavailability due to observed intestinal degradation of MOE compounds

¹ Radiolabel ³⁵S is associated with 5' end; Total radioactivity is measured

FIGURE 2

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**Bioavailability Analysis of Backbone Modified
Oligonucleotide Using Analogs of the
Phosphorothioate Oligonucleotide ISIS 4189**

ISIS 4189 CsAsGsCsCsAsTsGsGsTsTsCsCsCsCsCsAsAsc

ISIS 14182 CmAoGmCoCmAsTsGsGsTsTsCsCsCsCmCoCmAoAmC
3/3 MMI

ISIS 14183 CmAoGmCoCmAsImGoGmImCoCmCoCmCoCmAoAmC
Fully alternating PO/MMI

Key: s, P=S linkage; o, P=O linkage; m, MMI linkage

FIGURE 3

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MMI- Modifications Appear to Improve Oral Bioavailability of Oligonucleotides in Mice

Oligonucleotide	I.V.		Oral	
	Systemic Tissue ^a (%Dose)	Systemic Tissue ^a (%Dose)	Systemic Tissue ^a (%Dose)	% Bioavailability ^b
14182 MMI (3/3 P=O in the wings)	16.5		1.9	11.5
14283 MMI (alternating P=O throughout)	10.0		1.6	16.0c

^a (carcass- (skin+skeletal muscle)); 8 hours post dose

^b oral/I.V. x 100

^c may be overestimated due to rapid tissue clearance of this compound

FIGURE 4

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Prodrug Approach: SATE Oligomers

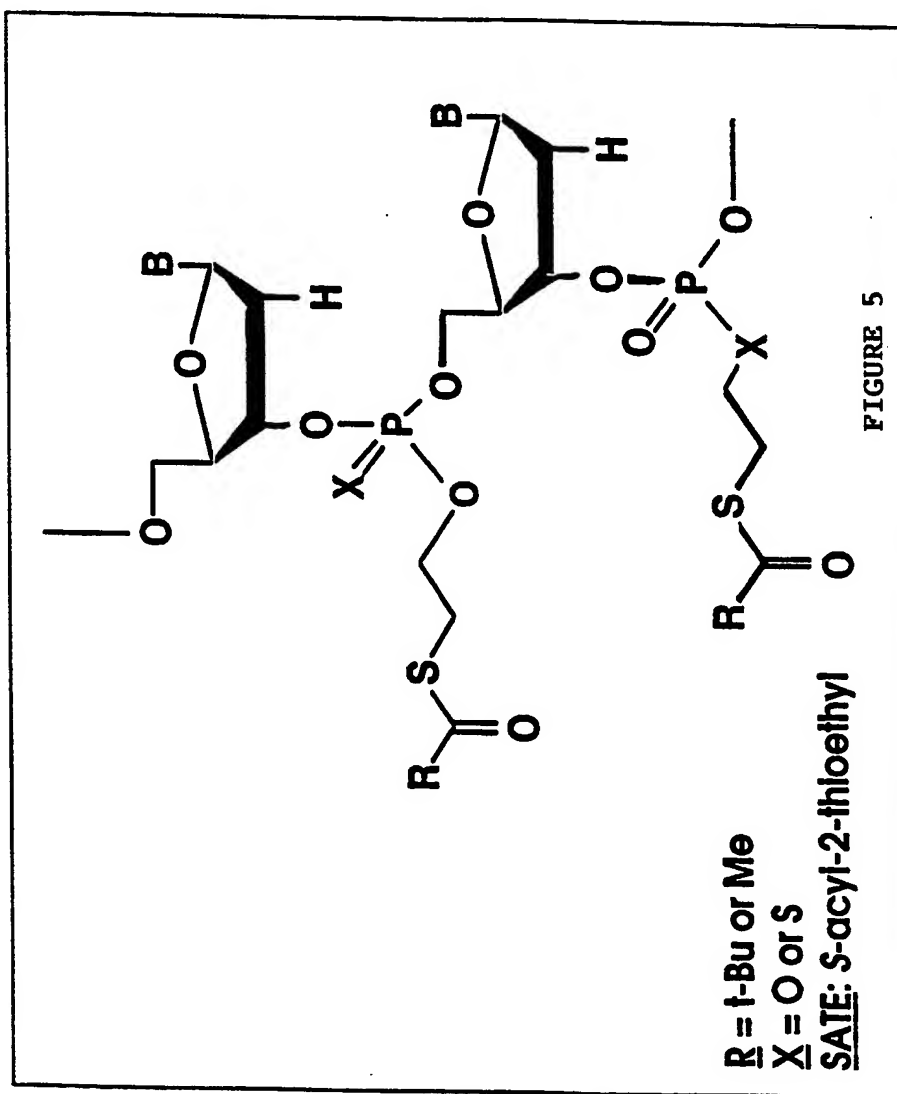


FIGURE 5

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Prodrug Modifications Appear to Improve the Oral Bioavailability of Phosphorothioate Oligonucleotides in Mice

Oligonucleotide	I.V.	Oral	
	Systemic Tissue ^a (% Dose)	Systemic Tissue ^b (% Dose)	% Bioavailability ^c
t-butyl SATE (T _{1/2} P=S)	42	10-18	9-16
t-butyl SATE (T _{1/2} P=O)	81	10-13	2.6-3.4

- a (liver + kidney) + (carcass); 1 hour post dose; total radioactivity
 b (liver + kidney) + (carcass); 1-4 hours post dose; total radioactivity
 c (oral/I.V. total radioactivity x oral/I.V. oligo associated radioactivity) x 100

FIGURE 6

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Intestinal Absorption of Methoxyethoxy Derivatives of ISIS 5132 / CGP 69846A Evaluated in Rat Model

ISIS 5132 TsCsCsCsGsCsTsGsTsGsAsCsAsTsGsCsAsTsI

CGP 69846A

ISIS 13650 IsCsCsCsGsCsTsGsTsGsAsCsAsTsGsCsAsTsI

CG# 1740

CGP 71849A

ISIS 12854 IoCoCoCoGoCsTsGsTsGsAsCsAsToGoCoAoIoI

CG# 1739

CGP 69845A

Key: A, C, G, I = 2' deoxyribose
 A, C, G, I = 2' MOE modified ribose
 o = phosphodiester
 s = phosphorothioate

FIGURE 7

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Rate of Absorption of Oligonucleotides in Different Sites of the Rat Intestine

Compound	Site	Absorption Rate ¹ (µg/min*cm)
5132	Duo/Jej	nd
	Ileum	0.2
	Colon	0.2
13650 ²	Duo/Jej	0.1
	Jejunum	0.8
	Ileum	0.7
	Colon	0.9
12854 ²	Duo/Jej	0.9 ²
	Duo/Jej	0.1
	Ileum	1.8
	Colon	1.7

^a Internally labeled with ³²S

¹ Absorption Rate = (amount of drug lost - amount bound to tissue/mucosa)/(time*length of intestinal segment); COMPARE WITH THEOPHYLLINE = 9 µg/min*cm

² Bile present; May be a confounding variable
nd not detectable

FIGURE 8